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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/743,184	11/1/96	VELAMAKER	30502/125

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EXAMINER	
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ART UNIT	PAPER NUMBER
1819	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/443,184	Applicant(s) Velander et al.
	Examiner Brian R. Stanton	Group Art Unit 1819

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-31 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the earlier filed application(s) in the first sentence of the specification (37 CFR 1.78).

This application repeats a substantial portion of prior Application No. 08/198,068, filed 2/18/94, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Claim Rejections - 35 USC § 112

Claims 1-11, 15-25, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of biologically active recombinant unmodified heterologous fibrinogen wherein each subunit of said fibrinogen is from the same species, does not reasonably provide enablement for the preparation of fibrinogen that is not unmodified or comprises heterologous subunit proteins derived from different species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the production of heterologous recombinant fibrinogen molecules because no guidance is present in regard to how one would have prepared a functional fibrinogen molecule that comprises subunit chains derived from different species. Similarly, the specification fails to provide an enabling disclosure for the production of fusion proteins or mutants/derivatives of fibrinogen proteins because the

specification fails to provide teachings regarding what such fusion proteins, mutants and derivatives would comprise, what activity such would have, and how one would have prepared any such proteins that have the appropriate biochemical activities such that they would have been useful as bioactive fibrinogen. As noted in the specification on page 2, at lines 13-32, fibrinogen is a heptameric protein comprising two copies each of three subunit chains that are linked by multiple disulfide bonds. This linker heptamer is then further post-translationally modified by glycosylation. The specification also states at page 2, lines 31 and 32 that, "(p)roper carbohydrate modification is required for functional activity of FIB". Therefore, the specification supports a conclusion that fibrinogen holoproteins are complex structures that require appropriate interchain linkages and post-translational modifications. If the subunit chains of the fibrinogen holoproteins was modified, it is unclear as to whether one would have been able to have generated functional fibrinogen molecules. Since the specification fails to provide any guidance as to how one would have prepared any alternative forms of fibrinogen molecules other than native fibrinogen, the artisan would have been required to have exercised undue experimentation in the practice of the full scope of the claimed invention and therefore limitation of the scope of the claimed invention to the production of full length, bioactive fibrinogen holoproteins wherein the subunits are derived from the same species is appropriate. It is noted that at page 10 of the specification a variety of modifications of fibrinogen are indicated. However, while one could have prepared alternative forms of fibrinogen subchains, no indication is present that any modified subchains would appropriately assemble into a functional fibrinogen molecule and the specification fails to disclose a use for non-bioactive fibrinogen molecules. In regard to the indication that the fibrinogen subunits must be from the same species, it is noted that since no teachings indicate that subunits from different species would properly interact to form a functional protein and since the structural requirements for such formation are highly restrictive as indicated by the specification, limitation to the use of subunits from the same species is appropriate.

The specification fails to provide an enabling disclosure for the production of fibrinogen in transgenic animals in any tissue other than mammary gland nor into any bodily fluid other than milk because the only teachings present in the specification that are directed to obtaining

expression of transgene products in any species other than milk are found at page 12, lines 12-17 wherein it is indicated that "(s)ignal sequences also can be used in accordance with this invention that direct the secretion of expressed proteins into other body fluids, particularly blood and urine, such as signal sequences for coagulation proteins such as protein C and Factor VIII". However, no indication of how one would have obtained or used such signal sequences is present in the as filed specification. Further, in order to garner expression in tissues other than mammary gland, appropriate promoters that direct *in vivo* expression to appropriate cells and organs would also have been required. However, the only promoters that are disclosed in the as-filed specification are those that are directed to obtaining gene expression in mammary glands. Therefore, the artisan would have been required to have exercised undue experimentation in preparing transgenic animals that express fibrinogen in tissues other than mammary gland and limitation to such express is therefore appropriate.

Claims 12-14, 26, 27, and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In regard to the inventions as defined by claims 12-14, 26, 27, and 29, it is noted that these claims are limited to the production of fibrinogen molecules that are either modified or fusion proteins (claims 12-14 and 29) or that are secreted into blood or urine (claims 26 and 27) and for reasons stated above in the basis of the rejection for failing to provide an enabling disclosure for the full scope of what is claimed, such inventions are not enabled by the teachings present in the as filed specification.

In regard to the invention of claims 30 and 31, it is noted that claim 30 refers to specific constructs that are defined both by plasmid designation and ATCC deposit number. However, since the specification fails to provide all the details for the preparation of such plasmids and since particular deposits are referenced, the claimed plasmids must be deposited in order to meet the requirements for enablement.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C. F. R. 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C. F. R. 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C. F. R. 1.809(d) should be added to the specification. See 37 C. F. R. 1.803 - 37 C. F. R. 1.809 for additional explanation of these requirements.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is vague and indefinite because it is incomplete and fails to reference the appropriate ATCC Accession numbers.

Claims 1 and 15 are vague and indefinite because it is unclear as to what is required for a protein to be considered to be "physiologically-functional".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Meade et al., 1989 (A1) or Rosen et al., 1994 (A14) either in view of Clark et al., 1988 (A4), Wyngaarden et al., 1988 (A21), Chung et al., 1983 (A7), Chung et al. (A8), and Rixon et al., 1983 (A9).

The claims under instant consideration are directed towards transgenic animals that comprise a heterologous fibrinogen gene under the control of a milk specific protein promoter. Embodiments of the claimed animals also comprise fusion genes of heterologous fibrinogen and milk proteins. Also claimed are methods of preparing proteins by harvesting body fluids of the aforementioned transgenic animals as a means of producing recombinant fibrinogen. It is noted that the term "physiologically functional" is unclear and therefore the instant ground of rejection is applicable to the claimed animals and methods of making fibrinogen to the extent that the artisan would have been motivated to have prepared fibrinogen molecules *per se* that did not have any particular activity requirement or limitation.

Each of Meade et al. and Rosen disclose means of producing transgenic animals that express transgenes in body fluids. Specifically, Meade et al. specifically disclose the preparation of animals that contain fusion genes wherein said fusion genes comprise a casein promoter fused

to a gene of interest (see e.g. Figure 1). Meade et al. also indicates that preferred transgenic hosts include cows, sheep, goats, mice, oxen, camels and pigs (see e.g. column 2, lines 57-68). In regard to the use of various promoters, Meade et al., teach that milk-specific promoters such as those of casein and beta lactoglobulin are particularly useful (see e.g. column 3, lines 1-15). Meade et al. also teach that the protein of interest may include a signal peptide such as those of milk-specific proteins (see e.g. column 3, lines 16-30) and that the "desired recombinant protein may be produced as a fused protein containing amino acids in addition to those of the desired or native protein. Meade et al. also disclose the isolation of milk from transgenic animals (see e.g. column 7, lines 5-21).

Rosen teaches the production of transgenic animals wherein said animals incorporate transgenes which are expressed in mammary glands. At column 2, lines 25-29, Rosen notes that the "ability to target genes to the mammary gland should result in efficient synthesis and secretion of proteins" and continues at lines 30-46 to state that "...proteins, hormones, drugs, lipids and carbohydrates can be synthesized and secreted". In regard to the design of recombinant DNA constructs useful in the construction of transgenic animals, Rosen notes that such DNA should "include a promoter, enhancer, signal peptide and coding sequences. In this combination the promoter, enhancer and signal peptide sequences are derived from mammary gland-specific genes and the coding sequence codes for a biological active agent...These sequences are derived from genes which are normally expressed only in mammary tissue. For example, these sequences can be obtained from genes which code for α-casein, γ-casein, ß-casein, κ-casein, α-lactalbumin, ß-lactoglobulin, and whey acidic protein". Rosen further discloses that the customized milk of transgenic animals prepared using the disclosed methods would be useful to produce a variety of biological active products (see e.g. column 10 at lines 12-17). Rosen also teaches that while many proteins may be synthesized in tissue culture, it is desirable to use transgenics rather than tissue culture because transgenic production of proteins of interest are more efficient at producing large amounts of proteins of interest.

Neither of Meade et al. nor Rosen teach the production of transgenic animals which produce fibrinogen.

Clark et al. also teach the use of animals for the production of pharmaceutical products and specifically address the advantage of generating animals that express transgene products in mammary glands. Clark et al. specifically indicates that one particularly useful set of pharmacologic agents that are desired to be produced in transgenic animals are those involved in coagulation such as Factor IX

Wyngaarden et al. teach the clotting cascade that includes fibrinogen (see e.g. page 1064, Figure 167-2) and also discloses that disorders involving lack of fibrinogen (afibrinogenemia) or altered fibrinogens (dysfibrinogenemia) may be treated by addition of fibrinogen in the form of cryoprecipitates of blood (see e.g. section entitled "Abnormalities in conversion of fibrinogen to fibrin" beginning on page 1073, second column and extending through the top of the first column on page 1074). Thus, it was recognized that fibrinogen treatment was desirable.

Rixon et al. teaches the structure and sequence of human α-chain fibrinogen (see e.g. Figure 2).

Chung et al. (A7) teaches the structure and sequence of the human ß-chain of fibrinogen (see e.g. Figure 3).

Chung et al. (A8) teaches the structure and sequence of the human ß-chain of fibrinogen (see e.g. Figure 2).

Given the fact that Meade et al. and Rosen teach the art recognized utility of preparing proteins of therapeutic value in transgenic animals and it was known that fibrinogen was a therapeutically important proteins, it would have been obvious to one of ordinary skill at the time of the invention to have prepared the claimed transgenic animals using art recognized promoters and constructs in combination with the art known fibrinogen genes so as to obtain therapeutic proteins in body fluids (such as the milk) of animals. In regard to the alternative body fluids cited in claims 24-26, it is noted that since transgene expression would have been expected to have occurred within the body, the product of said transgene would have been expected to have been present in a variety of body fluids and one would have harvested said product from any easily obtainable fluid such as blood or urine.

One would been motivated to prepare the claimed animals for the production of fibrinogen because one would have expected transgenic production of fibrinogen to be an efficient means of obtaining a pharmaceutically important compound.

Thus, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claims are allowable.

Interference

The following allowable claim is suggested for the purpose of an interference:

A method for producing biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bß chain, and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said egg into an oviduct or uterus of a female of said mammalian species to obtain offspring carrying said DNA segments;

breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin encoded by said segments;

collecting milk from said female progeny; and

and recovering the biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin from the milk.

The suggested claim must be copied exactly, although other claims may be proposed under 37 CFR 1.605(a).

Applicant should make the suggested claim within ONE MONTH or THIRTY DAYS from the date of this letter, whichever is longer. Failure to do so will be considered a disclaimer of the subject matter of this claim under the provisions of 37 CFR 1.605(a). THE PROVISIONS OF 37 CFR 1.136(a) DO NOT APPLY TO THIS TIME PERIOD.

Claims 15, 23, 25, and 28 are considered unpatentable over this suggested claim.

The following claim is considered allowable and directed to a separate patentable invention from the claim suggested above:

A transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin in its milk, wherein said mammal comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain,

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bß chain, and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, and

further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

The additionally suggested claim must be copied exactly, although other claims may be proposed under 37 CFR 1.605(a).

Applicant must also make this additionally suggested claim within ONE MONTH or THIRTY DAYS from the date of this letter, whichever is longer. Failure to do so will be considered a disclaimer of the subject matter of this claim under the provisions of 37

CFR 1.605(a). THE PROVISIONS OF 37 CFR 1.136(a) DO NOT APPLY TO THIS TIME PERIOD.

Claims 1, 2, 7, 9, and 10 are considered unpatentable over this additionally suggested claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached on Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Brian R. Stanton, Ph.D.
April 10, 1997

BRIAN R. STANTON
PRIMARY EXAMINER
GROUP 1800